ORIGINAL ARTICLE

SPREADING THROUGH AIR SPACES AND THINKING ABOUT LUNG METASTASES

Patrícia M. Castro[1*] , Joana Rei[1] , Cátia Silva[1], José Miranda[1], Miguel Guerra[1,2]

[1] Centro Hospitalar Vila Nova de Gaia/Espinho
[2] Faculdade de Medicina da Universidade do Porto

* Corresponding author: p.monteiro.castro@gmail.com

Abstract

Introduction: *Spread through air spaces (STAS) is a novel pattern of invasion in primary lung cancers, which was introduced in the 2015 World Health Organization classification. Several studies have validated STAS to be a predictor of clinical outcome in lung adenocarcinoma. However, little is known about STAS as a mode of intraparenchymal diffusion of pulmonary metastases (PMs).*

Objectives*: The aim of this study was to investigate the incidence of STAS among PMs and the association between STAS and clinicopathological characteristics of PMs.*

Methods: *From August 1, 2017 to July 31, 2022, 50 patients underwent pulmonary metastectomy in our center. Clinicopathological characteristics of patients were retrospectively evaluated. Continuous variables were compared by using unpaired Student´s t-test or MannWhitney test, as appropriate. Categorical variables were compared by using Qui-squared test or Fisher´s exact test as appropriate.*

Results: *A total of 50 patients with PMs who underwent surgical resection were analyzed, 68% being male. The median age of the study population was 60 years (range 24-80). Most patients had primary cancer originating from epithelial tissue (n=45) and the remaing from mesenchymal tissue (n=5). Colorectal cancer was the most frequent primary site of PMs (n= 32), followed by kidney (n=4) and osteosarcoma (n=3). 60% of patients (n=30) underwent sublobar resection (wedge resection or anatomic segmentectomy). STAS was observed in 10 patients (20%): 7 patients with PMs from CRC, 1 with PM from palatine tonsil, 1 from kidney and 1 from uterus. STAS was more frequent in elder patients (62 years, SD=7.099 vs 60 years, SD= 13.889; p = 0.034).*

Notably, STAS was significantly more frequent in PMs with larger dimension (2.8 cm, SD=2.049 vs 2.03 SD=1.104; p = 0.010), patients with lymph node metastases (p = 0.004) and in patients who underwent lobectomy rather than sublobar resection (70% vs 32.5%; p = 0.03). Although without statistically significant difference, locorregional recurrence and mortality was higher in patients with STAS+ (40% vs 22.5% and 40% vs 20%, respectively).

Conclusion: *VSTAS is nowadays considered to be a lung-specific tumour invasion pattern and is commonly observed in PMs of different origins.*

Keywords: *Spread through air spaces; lung cancer; pulmonary metastases; prognosis; recurrence*

INTRODUCTION

Spread through air spaces (STAS) is a novel pattern of invasion in primary lung cancers, which was introduced in the 2015 World Health Organization classification[1].

STAS is defined as micropapillary clusters, solid nests, or single cells spreading within air spaces beyond the edge of the main tumor[1]. STAS was initially observed in adenocarcinomas (ADC); however, recently, STAS was also identified in other types of lung cancer including squamous cell carcinoma (SQCC), pleomorphic carcinoma, invasive mucinous adenocarcinoma (IMA), neuroendocrine tumors and lymphoepithelioma-like carcinoma.

Several studies have validated STAS to be a predictor of clinical outcome in lung adenocarcinoma and demonstrated its association with worse prognosis[2,3]. However, if areas of incertitude and relatively poor evidence to support the definition have been evoked in the setting of lung cancer, even less is known about STAS as a mode of intraparenchymal diffusion of lung metastases[4].

METHODS

Data

We conducted a single-center and retrospective study including all consecutive subjects submitted to pulmonary metastectomy between August 1, 2017 to July 31, 2022 at Centro Hospitalar Vila Nova de Gaia/Espinho.

The preoperative, surgical and immediate postoperative data were retrospectively evaluated through the access of clinical files and computer registry system. Patients' records were analyzed up until the time of data collection in August 2022. All patients were operated on by the same surgical team.

To characterize our population, we collected data on patient's age, sex, tissue origin of primary cancer, tumor size, presence of lymph node metastases, number and laterality of pulmonary metastases and extension of pulmonary resection (lobar/sublobar).

Outcomes

Preoperative variables were analyzed within "STAS+" group and "STAS-" group. Continuous variables were compared by using unpaired Student´s t-test or MannWhitney test, as appropriate. Categorical variables were compared by using Qui-squared test or Fisher´s exact test as appropriate.

Statistical Analysis

The level of significance was set at 0.05. The IBM–SPSS Statistics version 26.0 (IBM, United States of America) program was used in data management and statistical analysis.

RESULTS

A total of 50 patients with PMs who underwent surgical resection were analyzed, 68% being male. The median age of the study population was 60 years (range 24-80). Most patients had primary cancer originating from epithelial tissue (n=45) and the remaining from mesenchymal tissue (n=5). Colorectal cancer was the most frequent primary site of PMs (n= 32), followed by kidney (n=4) and osteosarcoma (n=3). 60% of patients (n=30) underwent sublobar resection (wedge resection (n=28) or anatomic segmentectomy (n=2)) whereas 20 patients (40%) underwent lobectomy.

STAS was observed in 10 patients (20%): 7 patients with PMs from CRC, 1 with PM from palatine tonsil, 1 from kidney and 1 from uterus. STAS was more frequent in elder patients (62 years, SD=7.099 vs 60 years, SD=13.889; p= 0.034).

Notably, STAS was significantly more frequent in PMs with larger dimension (2.8 cm, SD=2.049 vs 2.03 SD=1.104; p=0.010), patients with lymph node metastases (p=0.004) and in patients who underwent lobectomy rather than sublobar resection (70% vs 32.5%; p=0.03). Although without statistically significant difference, locorregional recurrence and mortality was higher in patients with STAS+ (40% vs 22.5% and 40% vs 20%, respectively).

DISCUSSION

STAS is a relatively recent concept that has been identified as a novel mechanism of invasion[3]. There is an appealing evidence set associating the presence of STAS with lower survival and suggesting that STAS is an independent prognostic factor, regardless of the stage of tumour. [2,5-7] STAS represents the somewhat unconventional concept of air space invasion, which may be considered to be on pair with other more established patterns of invasive growth, such as lymphovascular or pleural invasion[8].

Lung is the most common metastatic site of various malignancy including colorectal cancer (CRC), osteogenic and soft tissue sarcoma, malignant melanoma, germ cell tumours, breast cancer and renal cell carcinomas. Pulmonary metastasectomy in carefully selected patients is now widely accepted as a curative intervention in the interdisciplinary management of metastatic malignancy[9]. Completeness of resection, primary tumour type and histology, disease-free interval, number and laterality of lung metastases and lymph node metastases were reported as prognostic indicators in patients who underwent pulmonary metastasectomy. However, local relapse occasionally occurs after lung resection, even after pathologically complete resection[10].

Several studies have demonstrated the adverse impact of the STAS-like pattern not only in lung cancer, but also in colon cancer metastatic to the lung. Patients whose metastatic tumors showed this feature had worse prognosis compared with those that did not have this feature[11,12]. Nevertheless, the association between STAS and recurrence patterns has not been clarified.

Clinicopathologically, STAS was reported to be associated with being male, a history of smoking, the presence of lymphovascular invasion, and more invasive subtypes such as micropapillary and solid patterns in patients with resected lung adenocarcinoma[13,14]. In our study, STAS was more frequently found in PMs with larger dimension and patients with lymph node metastases. Coincidentally, STAS was significantly more frequent in patients who underwent lobectomy rather than sublobar resection (70% vs 32.5%; p=0.03). These findings may be associated to the fact that larger tumors tend to undergo lobar resection rather than sublobar resection and that STAS, as previous mentioned, is related with lymphovascular invasion. These findings can also be a potential confounding factor to worse prognosis in STAS group. Several studies reported that anatomic segmentectomies represent a valid alternative to lobectomies, offering a better quality of postoperative life and a lower operative morbidity[15,16]. Thus, higher morbimortality observed in patients with STAS+ may potentially be related with greater proportion of lobectomies over sublobar resections in this group.

Table 1 **Clinicopathological characteristics**

	Total n=50	STAS + n=10	STAS - n=40	
VARIABLES	MEAN (SD) OR N(%)	MEAN (SD) OR N(%)	MEAN (SD) OR N(%)	P VALUE
Age, years	60 (12.779)	62 (7.099)	60 (13.889)	0.034
Masculine sex	34 (68%)	8 (80%)	26 (65%)	0.363
Tissue origin of primary cancer				0.569
Epithelial	45 (90%)	10 (100%)	35 (87.5%)	
Mesenchymal	5 (10%)	0 (0%)	5 (12.5%)	
Primary sites				0.347
Coloretum	32 (64%)	7 (70%)	25 (62.5%)	
Stomach	1 (2%)	0 (0%)	1 (2,5%)	
Testicle	2 (4%)	0 (0%)	2 (5%)	
Palatine tonsil	1 (2%)	1 (10%)	0 (0%)	
Kidney	4 (8%)	1 (10%)	3 (7.5%)	
Bladder	2 (4%)	0 (0%)	2 (5%)	
Uterus	1 (2%)	1 (10%)	0 (0%)	
Breast	2 (4%)	0 (0%)	2 (5%)	
Sarcoma	5 (10%)	0 (0%)	5 (12.5%)	
Tumour size (cm)	2 (1.256)	2.8 (2.049)	2.03 (1.104)	0.010
Lymph node metastases				0.004
+	2 (4%)	2 (20%)	0 (0%)	
-	48 (96%)	8 (80%)	40 (100%)	
Number of PMs				0.083
Solitary	36 (72%)	5 (50%)	31 (77.5%)	
Multiple	14 (28%)	5 (50%)	9 (22.5%)	
Laterality of PMs				0.470
Unilateral	48 (96%)	10 (100%)	38 (95%)	
Bilateral	2 (4%)	0 (0%)	2 (5%)	
Surgery				0.03
Sublobar resection	30 (60%)	3 (30%)	27 (67.5%)	
Lobectomy	20 (40%)	7 (70%)	13 (32.5%)	

Table 2

	Total n=50	STAS + n=10	STAS - n=40	
VARIABLES	MEAN (SD) OR N(%)	MEAN (SD) OR N(%)	MEAN (SD) OR N(%)	P VALUE
Mortality	13 (26%)	4 (40%)	9 (22.5%)	0.259
Locoregional recurrence	12 (24%)	4 (40%)	8 (20%)	0.185

Kadota et al.[1] and Shiono et al[6] previously showed that patients with STAS who underwent sublobar resection experienced a significantly higher incidence of locoregional recurrence and pulmonary metastasis compared to other patients, but they not clearly demonstrate that STAS is associated with PMs. Additionally, the results of Shiono et al suggested that STAS might also be a risk factor for pulmonary metastasis, but not a risk factor for extrathoracic metastasis. Thus, STAS is only associated with intrapulmonary metastasis, including that from surgical margins. However, how floating cancer cell clusters implant in the alveolar space remains unclear[6]. Given that alveolar macrophages can survive within air spaces for up to 40 days, it is conceivable that these free-floating tumour clusters can also remain viable in the alveolar space for extended periods of time[8]. Histologic evidence of the ability of tumor clusters that were once detached from the main tumor to subsequently reattach to alveolar walls and cause a stromal response in a distant location is also informative. There is the consistent and repeated finding that there is a significant association between the histological presence of free-floating tumour clusters and worse outcomes[8]. Further study of cell adhesion molecules is required to elucidate this phenomenon.

In a study performed by Y. Ma et al it was found that STAS exists in a broad spectrum of PMs with various types primary cancers, indicating that STAS might be a lung specific tumor invasion pattern. The incidence of STAS was significantly higher in PMs originating from epithelial tissues than those from mesenchymal tissues[10]. These finding were also observed in our study.

Takeda-Miyata et al.[17] found that STAS was related to poor prognosis and surgical margin relapse in PMs from CRC. Consistently, Yi Ma et al results showed that STAS was an independent risk factor for both recurrence-free survival (RFS) and worse overall survival (OS) in patients with PMs from CRC. Patients with STAS showed more frequent local relapse than those without STAS [10, 18, 19]. In this study, although without statistically significant difference, locorregional recurrence and mortality was higher in patients with STAS+ (40% vs 22.5% and 40% vs 20%, respectively).

Study limitations

There are some limitations in our study: 1) retrospective, single center experience limiting external validity and 2) relatively small sample size.

CONCLUSION

In summary, STAS is nowadays associated with poor prognosis and surgical margin relapse in PM. STAS may play a role as residual tumor cells, and, thus, more attention should be paid to such patients whose pulmonary metastases show this pattern. STAS is considered to be a lung-specific tumour invasion pattern and is commonly observed in PMs of different origins. Further investigation is needed in order to establish a correlation between worse prognosis, namely, locorregional recurrence and mortality, and the presence of STAS+.

Conflict of interest

There are no conflicts of interest.

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